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Health and Environmental Effects Profile for Chlorpyrifos and Chlorpyrifos-Methyl

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CHLORPYRIFOS AND CHLORPYRIFOS-METHYL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for chlorpyrifos and chlorpyrifos methyl was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Chlorpyrifos and chlorpyrifos methyl have been determined to be systemic toxicants. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for chlorpyrifos is $1x10^{-2}$ (mg/kg bw/day) and for chlorpyrifos methyl is $1x10^{-3}$ (mg/kg bw/day) for oral exposure.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
DNA	Deoxyribonucleic acid
GC	Gas chromatography
GI	Gastrointestinal
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
RBC	Red blood cells
RNA	Ribonucleic acid
SCE	Sister-chromatid exchange
STEL	Short-term exposure level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

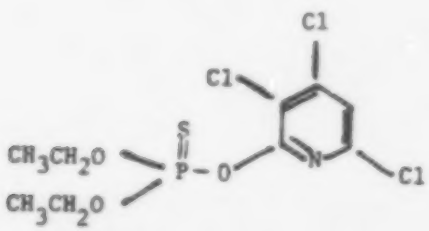
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Chlorpyrifos is the common name for O,O-diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate. It was introduced in 1965 by the Dow Chemical Company under the code number "Dowco 179" and the trademarks "Dursban" and "Lorsban" (BCPC, 1977). Synonyms for chlorpyrifos include chlorpyrifos-ethyl, Brodan, chloropyrifos, chlorpyriphos, Detmol U.A., Eradex, ENT 27311, Killmaster and OMS 971.

Chlorpyrifos-methyl is the common name for O,O-dimethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate. It was introduced in 1966 by the Dow Chemical Company under the code number "Dowco 214" and the trademark "Reldan" (BCPC, 1977). Synonyms for chlorpyrifos-methyl include Chlormethylfos, ENT 27520, Fospirate, M 3196, methyl chlorpyrifos, Methyl Dursban, Moltran, OMS 1155, Trichlormethylfos and Zertell.

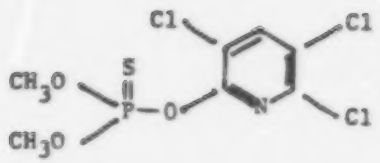
The structure and empirical formulae for chlorpyrifos and chlorpyrifos-methyl are as follows:



chlorpyrifos

Empirical formula: $C_9H_{11}Cl_3NO_3PS$

Molecular weight: 350.6



chlorpyrifos-methyl

Molecular formula: $C_7H_7Cl_3NO_3PS$

Molecular weight: 322.5

The Chemical Abstract Services (CAS) registry numbers for chlorpyrifos and chlorpyrifos-methyl are 2921-88-2 and 5598-13-0, respectively.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Chlorpyrifos and chlorpyrifos-methyl are both white crystalline solids with mild mercaptan odors at room temperature (BCPC, 1977). Selected physical properties of each are listed below.

Chlorpyrifos:

Melting point: 42.5-43°C (BCPC, 1977)

Vapor pressure: at 25°C: 1.87×10^{-5} mm Hg (BCPC, 1977)
at 35°C: 8.87×10^{-5} mm Hg (Brust, 1966)

Solubility:

Solvent	Temperature, °C	Solubility
iso-octane	35	790 g/kg (BCPC, 1977)
methanol	35	430 g/kg (BCPC, 1977)
water	35	2 ppm (BCPC, 1977)
water	20-25	0.4 ppm (Freed et al., 1979a)
water	20	0.3 ppm (Kenaga, 1980a)
water	20	0.7 ppm (Harris and Bowman, 1981)

Log octanol/water partition coefficient:	4.99 (Kenaga, 1980a) 3.31 (Rao and Davidson, 1982) 4.82 (Rao and Davidson, 1982) 5.11 (Rao and Davidson, 1982) 5.04 (McDuffie, 1981)
BCF factors:	
beef fat diet (average):	0.020 (Kenaga, 1980a)
fish (flowing water):	450 (Kenaga, 1980a)
fish (static water:	320 (Kenaga, 1980a)
Soil adsorption coefficient, K_{OC}:	13,600 (Kenaga, 1980a)

Chlorpyrifos-methyl:

Melting point:	45.5-46.5°C (BCPC, 1977)
Vapor pressure at 25°C:	4.22×10^{-5} mmHg (BCPC, 1977) 3.4×10^{-5} mmHg (Freed et al., 1979b)
Solubility in water at 25°C:	4 ppm (BCPC, 1977)
Log octanol/water partition coefficient:	3.29 (Rao and Davidson, 1982) 4.31 (Freed et al., 1979b) 4.17 (Kenaga, 1980a)
BCF factors:	
beef fat diet (average):	0.0046 (Kenaga, 1980a)
fish (flowing water):	430 (Kenaga, 1980a)
fish (static water):	95 (Kenaga, 1980a)
Soil adsorption coefficient, K_{OC}:	3300 (Kenaga, 1980a)

Chlorpyrifos is stable under normal storage conditions. Its half-life in aqueous methanolic solution at pH 6.0 is 1930 days, and at pH 9.96 is 7.2 days (BCPC, 1977; Spencer, 1968).

Chlorpyrifos methyl is also stable under normal storage conditions. It is relatively stable in a neutral medium, but hydrolysis occurs in both acid (pH 4-6) and basic (pH 8-10) media. The rate of hydrolysis is more rapid under basic conditions (BCPC, 1977).

1.3. PRODUCTION DATA

Chlorpyrifos and chlorpyrifos-methyl are made by the reaction of 3,5,6-trichlor-2-pyridinol with O,O-diethyl- and O,O-dimethyl phosphorochloridothioate, respectively (BCPC, 1977; Spencer, 1968).

The only domestic producer of chlorpyrifos is Dow Chemical in Midland, Michigan (SRI, 1983; USITC, 1983). Current production figures are not available. The capacity of Dow's manufacturing facility is reported to be 8 million lb/year (SRI, 1976).

1.4. USE DATA

Chlorpyrifos and chlorpyrifos-methyl are used as insecticidal agents, and are effective by contact, ingestion and vapor action (BCPC, 1977). They are used for the control of mosquitoes (larvae and adults), flies, various soil, and many foliar crop pests and household pests.

Use of chlorpyrifos on major field and forage crops was 5.1 million pounds in 1982, but <50,000 pounds in 1976 and 1971 (U.S. Department of Agriculture, 1983). In 1982, 3.9 million pounds of chlorpyrifos were used in corn fields (U.S. Department of Agriculture, 1983). In 1975, total domestic consumption of chlorpyrifos was reported to be 4.0 million pounds with use of 2.0, 1.0 and 1.0 million in lawn and turfs, ornamentals and commercial-household-industrial establishments, respectively (SRI, 1976).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESS

2.1. WATER

2.1.1. Chlorpyrifos. The environmental fate of chlorpyrifos in water depends upon its ability to undergo chemical, photochemical and microbial reactions and partition between the sediment and the atmosphere. The hydrolysis half-life of chlorpyrifos in a buffered solution at pH 7.4 is 53.0 days at 20°C and 13.4 days at 37.5°C (Freed et al., 1979a). At pH 6.1 and 20°C, the hydrolytic half-life is 120 days (Freed et al., 1979c). Macalady and Wolfe (1981) found that the neutral hydrolysis of chlorpyrifos at 25°C in distilled water proceeds with a rate constant of 4×10^{-6} min^{-1}, which is equivalent to a half-life of 120 days. Disappearance rates of chlorpyrifos from natural water samples at 25°C were found to be 2-200 times faster than the distilled water value; neither pH effects, trace mineral catalysis, nor microbes could account for the accelerated degradation. Blanchet and St. George (1982) found that the rate of hydrolysis of chlorpyrifos and chlorpyrifos-methyl increased with increasing Cu(II) ion concentration and pH. Mortland and Raman (1967) also found that the Cu(II) ion enhanced the hydrolysis of chlorpyrifos. Schaeffer and Dupras (1970) reported that the hydrolysis rate in pond water increased with increasing temperature from 10-38°C. Meikle and Youngson (1978) determined that the hydrolysis rate of chlorpyrifos in water followed first-order kinetics over the concentration range 3×10^{-9} M to 3×10^{-7} M. In buffered distilled water, the following half-lives (in days) were determined:

	15°C	25°C	35°C
pH 4.7	210	62.7	16
pH 6.9	99	35.3	11.5
pH 8.1	54	22.8	4.5
pH 8.0 (canal water)	-	1.5	-

Hydrolysis was significantly faster in canal (natural) water than in distilled water. Meikle and Youngson (1978) also identified the products of chlorpyrifos hydrolysis:

(I) 3,5,6-trichloro-2-pyridinol

(II) O-ethyl O-hydrogen O-(3,5,6-trichloro-2-pyridyl) phosphorothioate

(III) O,O-dihydrogen O-(3,5,6-trichloro-2-pyridyl) phosphorothioate

Meikle et al. (1983) found that the combined photolysis-hydrolysis rate of chlorpyrifos in distilled water at 25°C followed simple first-order kinetics at the initial concentration of 9×10^{-7} M. In the buffered distilled water at pH 5.0, 6.9 and 8.0, the combined photolysis-hydrolysis half-lives were determined to be 11.0, 12.2 and 7.8 days, respectively. The photolysis was initiated by a series of black lights emitting irradiation in the environmentally significant range of $\geq$290 nm. Subtracting the hydrolysis-only rate constants for chlorpyrifos as determined by Meikle and Youngson (1978), the half-life of the isolated photolysis reaction at pH 5.0, 6.9 and 8.0 is 13.9, 21.7 and 13.1 days, respectively. Meikle et al. (1983) identified the products of the combined photolysis-hydrolysis of ^{14}C-chlorpyrifos (2,6-ring-labeled) to be O-ethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothiate, 3,5,6-trichloro-2-pyridinal, and five radioactive unknowns, one of which likely contains $H^{14}CO_3^-$. Smith (1968) studied the decomposition of chlorpyrifos in a methanol-water (1/1) system under irradiation with sunlamps, and determined that ~50% of the chlorpyrifos was reacted (due to chemical and photochemical decomposition) in 25 days at pH 7, in 29 days at pH 5 and in 108 days at pH 9. The difference between this study and that of Meikle et al. (1983) may be the use of different light sources. Extrapolation of these data to the environment is difficult, since intensity and incident wavelength were not reported.

Sharom et al. (1980a) examined the relative importance of chemical vs. biological degradation of chlorpyrifos by comparing the persistence in natural, distilled, sterilized natural and sterilized distilled waters at laboratory conditions of 21°C, storage in the dark and initial concentration of 5 ppm. The results indicated that microbial degradation of chlorpyrifos is of minor importance, as the degradation was only slightly faster in the unsterilized waters. Degradation in the natural waters was about twice as rapid as in the distilled waters during the initial 4 weeks of the study; ~50% of the initial chlorpyrifos was lost in natural waters compared to ~25% in the distilled waters. As noted in Section 2.3., it has been demonstrated that soil microorganisms can degrade chlorpyrifos. The above study by Sharom et al. (1980a) did not include sediment found in the natural waters.

Data specific to the transport of chlorpyrifos from the aquatic environment due to volatilization were not located in the available literature. Meikle et al. (1983) has shown that chlorpyrifos can volatilize rapidly from inert surfaces. Getzin (1981a) found that volatilization of chlorpyrifos became increasingly important in soil as the water saturation point was approached. Neely (1979) estimated that 6% of applied chlorpyrifos will transport to the air in a simulated ecosystem using experimental values for rate constants. Swann et al. (1983) has reported that the water-to-air ratio (K_w) for a chemical can be estimated by the following equation:

$$K_w = \frac{(0.0624)(WS)(T)}{(VP)(MW)}$$

where

WS is water solubility (ppm)
T is temperature (°K),
VP is vapor pressure (mmHg)
MW is molecular weight (g/mole).

For chlorpyrifos, the water-to-air ratio is on the order of 1000:1.

The transport of chlorpyrifos in aquatic systems due to adsorption on sediment appears to be an important mechanism. Hughes et al. (1980) applied chlorpyrifos to a series of polyethylene-lined ponds and a natural pond. It was observed that a rapid partitioning took place following application, and that the rapid initial disappearance of chlorpyrifos from the water was primarily attributable to adsorption on bottom sediments and polyethylene. Concentration of chlorpyrifos in the sediments rose for several days and then began to decline. Hurlbert et al. (1970) noted that the level of chlorpyrifos in the mud of natural ponds to which it was applied increased to a maximum 7 days after application and then declined. Neely (1979) estimated that at certain times in a simulated ecosystem, as much as 4 times more chlorpyrifos can be present in the soil-phase as in the water-phase. Data presented in Section 2.3. indicate that chlorpyrifos is tightly adsorbed by the organic matter in soils. The desorption of chlorpyrifos by the sediment can contribute to the residual concentrations in the water (Hughes et al., 1980). Schaefer and Dupras (1970) observed that adsorption onto organic solids caused most of the chlorpyrifos to leave the water-phase during the first few days following application at a sewage treatment holding pond.

Kenaga (1980a) reported the following experimental BCFs for chlorpyrifos:

fish (flowing water):	450
fish (static ecosystem):	320

Kenaga (1980b) predicted that the BCFs for chlorpyrifos, based on water solubility and soil adsorption coefficient equations, are 1220 and 1100, respectively.

The persistence of chlorpyrifos in the aquatic environment has been studied by a number of investigators. Table 2-1 summarizes various

TABLE 2-1

Persistence Studies on Chlorpyrifos in the Aquatic Environment

Results of Study	Reference
Chlorpyrifos was applied to four artificial outdoor ponds during the summer months. A half-life of 5 hours was determined for an emulsifiable formulation and a half-life of 14 hours for a slow-release granular formulation.	Reimer and Webster, 1980
Reported that the half-life of chlorpyrifos in pasture water under summer field conditions was 6-7 hours. However, in polluted waters with high organic content, adsorption caused relatively long-term residual concentrations. Degradation was found to increase with increasing temperatures.	Schaefer and Dupras, 1970
After 8 hours in sewage water, most of initial application of chlorpyrifos was still present. Degradation was possibly delayed by adsorption onto organic matter.	Schaefer and Dupras, 1972
Application of 10 ppb chlorpyrifos to a natural pond resulted in 90% of chlorpyrifos leaving water-phase in 1.6 days, mostly due to adsorption. After 1 day, concentration in sediment rose to ~350 ppb. Sediment concentration was ~100 ppb after 11 days.	Hughes et al., 1980
Aerial application of chlorpyrifos at 0.025 and 0.05 lb/acre to a salt-marsh resulted in concentrations in water samples averaging 3.8 and 5.4 ppb, respectively, 1 hour after spraying. At 0.025 lb/acre, chlorpyrifos was not detectable after 7 days. At 0.05 lb/acre, levels fell to 0.4 ppb after 1 day and were not detectable 13-21 days after application.	Ludwig et al., 1968
Chlorpyrifos was applied to small ponds in California at varying concentrations. At the highestconcentration (0.2 ppm or 1.0 lb/acre), the mean levels in the water after 1 day, 2 days, 7 days and 14 days were 0.097, 0.068, 0.006 and <0.004 ppm, respectively. Residual levels in the mud increased from 0.01 ppm after 4 hours to 0.3 ppm at 7 days.	Hurlbert et al., 1970

persistence studies relevant to chlorpyrifos. Hydrolysis-photolysis persistence data from Meikle et al. (1983) and Meikle and Youngson (1978) were discussed previously; these authors concluded that the degradation rate of chlorpyrifos in the water is sufficiently fast that it will not persist in bodies of water. Since chlorpyrifos adsorbs strongly to sediments and suspended solids, however, the photolysis and hydrolysis rates determined in the laboratory will be higher (faster) than those in the environment. Consequently, extrapolation of laboratory data to the environment is difficult.

2.1.2. Chlorpyrifos-methyl. The chemical hydrolysis rate of chlorpyrifos-methyl in a buffered solution of pH 7.4 (measured as a half-life via first-order kinetics), is 12.5 days at 20°C and 2.6 days at 37.5°C (Freed et al., 1979a). At pH 6.1 and 20°C, the hydrolytic half-life is 26 days (Freed et al., 1979c). Blanchet and St. George (1982) found that the rate of hydrolysis of chlorpyrifos-methyl increased with increasing Cu(II) ion concentration and pH. Meikle and Youngson (1978) determined the following hydrolysis half-lives in days for chlorpyrifos-methyl in buffered distilled water and canal water:

	15°C	25°C	35°C
pH 4.2	75	22.8	7.4
pH 6.7	54.5	17.4	5.3
pH 7.8	45	12.7	4.8
pH 8.0 (canal water)	25	9.4	3.6

The hydrolysis proceeds faster in natural (canal) water than in distilled water, indicating that something present in the natural water is catalyzing the reaction. Meikle and Youngson (1978) identified the following hydrolysis products at pH 6.7 and 35°C after 359 hours:

(I) 3,5,6-trichloro-2-pyridinol

(II) O-hydrogen O-methyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate

Data specific to the photolysis of chlorpyrifos-methyl were not located in the available literature. Chlorpyrifos has been found to be significantly photolabile.

Data specific to the microbial degradation of chlorpyrifos-methyl were not located in the available literature. Szeto and Sundaram (1982) suggested that soil microorganisms may have some significance in chlorpyrifos-methyl degradation in flooded soils.

In an environmental-chamber aquatic ecosystem, Szeto and Sundaram (1982) reported that very little of the chlorpyrifos-methyl present in the water was lost to the atmosphere due to volatilization transport. The water-to-air ratio, as calculated from the previously listed equation from Swann et al. (1983), is ~6000:1.

The transport of chlorpyrifos-methyl in aquatic systems due to adsorption by sediment appears to be an important mechanism. Szeto and Sundaram (1982) examined the behavior of chlorpyrifos-methyl in two laboratory aquatic models. In both systems, the chlorpyrifos-methyl was strongly adsorbed by flooded soils. It was noted that little desorption occurred prior to degradation. Hughes et al. (1980) applied chlorpyrifos-methyl to a series of polyethylene-lined ponds and a natural pond, and observed that a rapid partitioning took place following application. The rapid initial disappearance of chlorpyrifos-methyl from the water was primarily attributable to adsorption on bottom sediments and polyethylene. The concentration of chlorpyrifos-methyl in the sediments rose for several days and then began to decline. Szeto and Sundaram (1981) examined stream water and sediment following an aerial spraying of chlorpyrifos-methyl, and found that it was not

detectable in the water-phase after 4 days, but persisted in the sediments for 10 days. Data presented in Section 2.3. indicate that chlorpyrifos-methyl is tightly adsorbed by the organic matter in soils.

Kenaga (1980a) reported the experimental BCF for chlorpyrifos-methyl in fish (static ecosystem) as 95. Kenaga (1980a) also reported a BCF value of 430 for fish (flowing water) as a calculated value. Kenaga (1980b) predicted that the BCFs for chlorpyrifos-methyl, based on water solubility and soil adsorption coefficient equations, are 280 and 230, respectively.

The persistence of chlorpyrifos-methyl in the aquatic environment has been studied by several investigators. Szeto and Sundaram (1982) examined the degradation of chlorpyrifos-methyl in two aquatic model studies in the laboratory. In the first study, a sandy loam soil was given a chlorpyrifos-methyl concentration of 423 ppb and then covered with lake water in an aquarium and held at 15°C for 90 days. The maximum concentration of chlorpyrifos-methyl detected in the water-phase was 1.0 ppb and occurred 0.7 days after incubation. It was not detectable (limits of 0.05 ppb) in the water after 37 days. Concentration in the soil after 1, 10, 37 and 90 days was 287, 180, 61.2 and 8.0 ppb, respectively. In the second study, untreated soil was put in the aquarium and covered with lake water, which was subsequently given a concentration of 200 ppb chlorpyrifos-methyl and held at 15°C for 83 days. The concentration of chlorpyrifos-methyl in the water in ppb at the indicated time after incubation was: 180 (1 day), 90 (6 days), 40 (14 days), 6.8 (30 days) and 0.1 (83 days). The concentration in the soil rose to a maximum of 562 ppb after 13 days and declined to 13.1 ppb after 83 days. In both studies, 3,5,6-trichloro-2-pyridinol was monitored

as the major metabolite. As noted previously, Szeto and Sundaram (1981) reported that chlorpyrifos-methyl dissipated rapidly in stream water after its aerial application. Hughes et al. (1980) applied 10 ppb chlorpyrifos-methyl to artificial polyethylene-lined ponds and found that 90% of the initial concentration left the water-phase in 1.2 days. After 11 days, it was not detectable in the water. Concentrations on the polyethylene lining rose to ~400 ppb after 1 day and fell to ~15 ppb after 11 days.

2.2. AIR

2.2.1. Chlorpyrifos. Klisenko and Pis'mennaya (1979) reported that the photolysis of chlorpyrifos in the air is a first-order reaction with a half-life of 136 minutes. As noted in Section 2.1.1., chlorpyrifos is significantly photolabile in aqueous solution. Brust (1966) reported that exposure of solid chlorpyrifos to UV radiation turns it yellow after 44 hours and dark brown after 300 hours. It would, therefore, seem likely that photolysis is the significant degradation mechanism for chlorpyrifos in the air; however, data specific to other fate and transport mechanisms were not located in the available literature.

2.2.2. Chlorpyrifos-methyl. Data pertinent to the fate and transport of chlorpyrifos-methyl in the atmosphere could not be located in the available literature.

2.3. SOIL

2.3.1. Chlorpyrifos. The environmental importance of the photodecomposition of chlorpyrifos from soil surfaces is not clear. Getzin (1981a) reported that neither UV light nor sunlight altered the stability of chlorpyrifos on dry soil surfaces, and neither oxidation nor ring cleavage was demonstrated after exposing chlorpyrifos-treated soil surfaces to UV light or sunlight for 8 days. Meikle et al. (1983) deposited chlorpyrifos on

filter paper, covered it with carnuba wax to prevent volatilization, and exposed it to UV irradiation in the environmentally significant spectra ranges. A half-life of 3.2 days was determined. Brust (1966) reported that exposure of solid chlorpyrifos to UV radiation turns it yellow in 44 hours and dark brown in 300 hours. Smith (1968) exposed dry chlorpyrifos to a sunlamp for 1200 hours and found that <2% of it decomposed.

The chemical hydrolysis of chlorpyrifos on air-dried soil surfaces and soil clays has been reported by Getzin (1981a). The hydrolysis was found to be a clay-activated catalytic reaction yielding 3,5,6-trichloro-2-pyridinol as a primary degradation product. Getzin (1981a) used ^{14}C-ring-labeled chlorpyrifos to measure the combined dissipation (due to hydrolysis and volatilization) from various soil surfaces and clays. The importance of hydrolysis on air-dried silt loam soil after 20 days of incubation was demonstrated by the following results:

Temperature, °C	Chlorpyrifos Total dissipation, %	Dissipation due to Hydrolysis, %
5	20	19
15	40	35
25	65	59
35	85	72
45	95	84

Hydrolysis was found to be more rapid on air-dried surfaces of calcium homoionic clays such as illite, vermiculite and kaolinite, and clay isolated from the silt loam soil. The hydrolysis was slower on a sandy loam, monmorillonite, or on an organic soil, and negligible on peat moss and quartz sand. As water was sorbed onto the air-dried surfaces, the clay-catalyzed hydrolysis rate decreased. The relative importance of the hydrolysis or volatilization processes depended upon the amount of sorbed moisture.

The significance of microbial degradation of chlorpyrifos in soils has been demonstrated. Getzin (1981b) compared the decomposition of ^{14}C-ring-labeled chlorpyrifos in a clay loam and a silt loam soil vs. the decomposition in the same soils that had been sterilized by autoclaving. The initial half-life of the chlorpyrifos in the nonsterile soils was 4 weeks (clay loam) and 12 weeks (silt loam), while the initial half-life in both sterilized soils was 24 weeks. Radioactivity from the decomposed chlorpyrifos was recovered as expired CO_2, as 3,5,6-trichloro-2-pyridinol and as unextractables. After 32 weeks of incubation in the nonsterile clay loam, ~50% of the radioactivity was recovered as CO_2, indicating significant microbial degradation of the chemical metabolites as well as the chlorpyrifos itself. Miles et al. (1979) compared the persistence of chlorpyrifos (10 ppm) in both sterile and nonsterile sandy loam soil and organic soil. The initial half-lives in the sterile sandy loam and organic soil were 17 and 40 (graph-derived) weeks, respectively, while the initial half-lives in the nonsterile soils were <1 week and 2.5 weeks, respectively. Getzin and Rosefield (1968) sterilized a clay loam soil by two different methods, autoclaving and gamma irradiation, and compared the degradation of chlorpyrifos in both the sterilized soils and in a nonsterilized sample of the same clay loam. After 4 weeks of incubation, 33 and 38% of the chlorpyrifos had been degraded in the autoclaved and irradiated soils, respectively, while 62% had been degraded in the nonsterile soil sample. Munnecke (1981) reported that chlorpyrifos is subject to enzymatic hydrolysis by cell-free enzyme preparations derived from microorganisms.

The transport of chlorpyrifos from soil surfaces can be significant. As noted before, Getzin (1981a) examined the dissipation of chlorpyrifos from soil surfaces due to volatilization and clay-catalyzed hydrolysis. Getzin

(1981a) found that as the sorbed water content approached the saturation point, volatility became increasingly important in the loss of chlorpyrfos from the soil surface. On organic soils and at high sorbed moisture levels on mineral soils, volatility was considered to be the probable dominant dissipation mechanism. Meikle et al. (1983) measured the volatility of chlorpyrifos from a filter paper strip at 25°C, in the dark, with an air movement of 0.2 mph. The volatilization half-life was determined to be 7.8 hours, or ~10 times faster than the photodecomposition half-lives determined from the same surface.

The mobility or leaching of chlorpyrifos in the soil has been examined by a number of authors. Table 2-2 lists various mobility studies of chlorpyrifos. As can be noted from the data in Table 2-2, chlorpyrifos is generally immobile in soil, particularly in soils with high organic matter content.

As with mobility, the persistence of chlorpyrifos in the soil has been studied by a number of authors. Table 2-3 lists various persistence studies of chlorpyrifos. The persistence of chlorpyrifos in nonsterile vs. sterile soils has already been discussed (Getzin, 1981b; Getzin and Rosefield, 1968; Miles et al., 1979). Soil-incorporated chlorpyrifos is more persistent than surface-applied chlorpyrifos.

2.3.2. Chlorpyrifos-methyl. Data pertinent to the hydrolysis, photolysis and microbial degradation of chlorpyrifos-methyl in soil were not located in the available literature. As noted previously, chlorpyrifos has been shown to be photolabile and to undergo clay-catalyzed hydrolysis in soil. Therefore, it is possible that chlorpyrifos-methyl will also undergo hydrolysis in soil and photolysis at the surface at environmentally significant rates.

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TABLE 2-2

Literature Considering Mobility-Leaching of Chlorpyrifos

Results of Study	Reference
Reported soil adsorption coefficients, K_{oc} values of 13,600 (experimental) and 8,500 (calculated), indicating that chlorpyrifos is tightly bound to organic matter in soil and considered immobile.	Kenaga, 1980a,b
Applied chlorpyrifos to a loam soil and periodically irrigated the soil by overhead sprinklers. Greater than 99% of the chlorpyrifos remained in the upper 2.5 cm of soil, indicating relative immobility.	Pike and Getzin, 1981
Chlorpyrifos was readily adsorbed by sandy loam and organic soils in the laboratory and was relatively resistant to desorption. A calculated mobility factor indicated chlorpyrifos was relatively immobile in the soil tested and least mobile in the organic soil.	Sharom et al., 1980b
Applied chlorpyrifos to turfgrass at recommended rates. Less than 1% of initial chlorpyrifos was detected in the 2.5 cm soil underlying the grass at any time throughout the 56-day test period.	Sears and Chapman, 1979
Chlorpyrifos was adsorbed to a greater extent as the organic matter content of the soil increased. The average K_{om} value for five tested soils was 2645.	Felsot and Dahm, 1979
Soil columns were used to test the leaching of chlorpyrifos in three agricultural soils. The average K_{oc} value in the soils was 6070. The columns were eluted with 20 acre-inches of water and the chlorpyrifos leached only 0.5-1.0 cm.	McCall et al., 1980, 1981; Swann et al., 1981
Chlorpyrifos was applied in a band at 1.5 kg/ha to a soil. No horizontal movement was observed from the band.	Agnihotri et al., 1981

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TABLE 2-3

Literature Considering Chlorpyrifos Persistence in the Soil

Results of Study	Reference
Residues of chlorpyrifos persisted for 180 days after being applied in a band at 1.5 kg/ha to a field soil.	Agnihotri et al., 1981
Chlorpyrifos was applied at 2.0 kg/ha to a paddy soil and dissipated to 50% of the initial deposit after 10 days. Sixty days after treatment, 0.84 ppm were still present in the soil.	Gary and Sethi, 1980
Chlorpyrifos was applied at 3.4 kg/ha and incorporated into sandy and muck soils in field plots. The initial half-lives were 2 and 8 weeks, respectively, in the sandy and muck soils, 4% and 9% remained after 1 year. 3,5,6-Trichloro-2-pyridinal was the major degradation product.	Chapman and Harris, 1980
Chlorpyrifos sprayed at 1 kg/ha on a soil surface showed a half-life of 1 month.	Leoni et al., 1981
The half-lives of chlorpyrifos in a moist clay loam soil at 0.1 ppm and 1.0 ppm under laboratory conditions were both 120 days.	Freed et al., 1979c
Chlorpyrifos was applied at 2.24 kg/ha to bluegrass turf. The half-life on the grass was ~1 week. Chlorpyrifos residues in the soil were >1 ppm after 6 weeks.	Kuhr and Tashiro, 1978
Laboratory bioassays of soils from treated field plots showed that chlorpyrifos disappeared faster with soil surface treatments than with subsurface or incorporated applications.	Read, 1976
Chlorpyrifos was applied at recommended rates to turfgrass. Only 9% remained 56 days after treatment.	Sears and Chapman, 1979
Residues of chlorpyrifos in organic soil following surface treatment were 18.6 ppm immediately after treatment, 5.1 ppm 1 month later and 5.0 ppm ~3.5 months after treatment.	Harris et al., 1973a

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TABLE 2-3 (cont.)

Results of Study	Reference
Residues of chlorpyrifos in soil following application to rye foliage were 0.18 ppm immediately after treatment, 0.04 ppm 24 days later and 0.003 ppm just over 4 months after treatment.	Harris et al., 1973b
Chlorpyrifos was applied at 2.2 kg/ha as a surface-spray to a loam soil. Irrigation was applied at various intervals by sprinklers or not at all. Persistence was found to be least in the non-irrigated field plots. Dissipation rates were rapid during the 2 weeks after application and then proceeded more slowly. The initial halflife in the non-irrigated plots was 8-14 days with ~30% of the original concentration remaining after 50 days.	Pike and Getzin, 1981
A field study on silt loam soil showed that chlorpyrifos disappeared 2-3 times faster from a soil surface which was generally dryer than when it was incorporated or applied beneath the surface. Other data presented in text of Section 2.3.1.	Getzin, 1981a

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Szeto and Sundaram (1982) suggested that soil microorganisms may contribute significantly to the degradation of chlorpyrifos-methyl and its toxic metabolites due to the disparity of degradation data generated by them as compared to Meikle and Youngson (1978). Meikle and Youngson (1978) reported that 45.1% of chlorpyrifos-methyl added to canal water remained after incubation at 15°C for 29 days, while Szeto and Sundaram (1982) found that <10% remained in lake water covering soil after 30 days incubation at 15°C. Soil microorganisms may account for the difference.

The available data regarding leaching of chlorpyrifos-methyl indicate that it is relatively immobile in soil. Kenaga (1980b) reported that the soil adsorption coefficient (K_{oc}) for chlorpyrifos-methyl is 3300 as an experimental value, and 2000 as a calculated value. Both values indicate that chlorpyrifos-methyl is quite tightly bound to organic matter in soil and is therefore considered immobile. Data presented in Section 2.1.2. demonstrated that chlorpyrifos-methyl was partitioned significantly into the sediment portion of natural water.

Swann et al. (1983) has reported that the volatility rate from soil surfaces is directly proportional to the vapor pressure, and inversely proportional to the water solubility and soil adsorption coefficient, K_{oc}. This indicates that in soils with high organic content, the tight adsorption to the organic matter would limit the volatilization rate. In sandy soils, however, or in other soils or conditions lacking adsorptive sites, the volatilization rate may become increasingly environmentally significant.

Data specific to the persistence of chlorpyrifos-methyl in soil could not be located in the available literature.

3. EXPOSURE

Most of the data presented in this section are specific to chlorpyrifos; only limited monitoring data are available for chlorpyrifos-methyl.

3.1. WATER

The U.S. EPA STORET data base reports the analysis of chlorpyrifos in 198 whole water and 11 water samples (these are probably the same type of samples). The mean concentration of chlorpyrifos in both the whole water and water samples was 0.9 µg/ℓ, with a range of 0.04-1.0 µg/ℓ. Eight dry sediment samples were analyzed for chlorpyrifos and found to have a mean concentration of 2.77 mg/kg, with a range of 0.02-20 mg/kg.

Braun and Frank (1980) collected 949 stream water samples from 11 agricultural watersheds in southern Ontario during 1975 and 1977, and analyzed the samples for organochlorine and organophosphorus insecticide residues that were currently in use in those watersheds. Chlorpyrifos was present in only three samples. Maddy et al. (1982) collected well water samples from 27 private and municipal wells in California. The samples were analyzed by an organophosphate screening method and chlorpyrifos was detected; the number of samples in which chlorpyrifos was detected was not given, nor were its concentrations.

Ludwig et al. (1968) monitored chlorpyrifos concentrations in a salt marsh to which chlorpyrifos was applied by aerial spraying to kill mosquitos. Residues in water samples of the treated marsh averaged 0.0038 ppm 1 hour after application, and were not detectable 7 days after treatment of 0.025 lb/acre. One hour after application of 0.05 lb/acre, chlorpyrifos concentrations averaged 0.0054 ppm.

Szeto and Sundaram (1981) monitored the concentration of chlorpyrifos-methyl in stream water after two aerial sprayings of 70 g/ha to a coniferous

forest. More than 90% of the chlorpyrifos-methyl had disappeared from the stream water 3 hours after treatment, and none was detected after 4 days.

3.2. FOOD

Duggan et al. (1983) compiled the results of pesticide residue monitoring for the Fiscal Years 1970-1976 from three Federal monitoring programs: the Total Diet Program in which 1980 food composites of ready-to-eat foods were analyzed, the FDA Monitoring Program for raw agricultural commodities in which 33,000 domestic and 18,000 imported samples were examined, and the USDA National Residue Program in which 15,000 red meat and 11,000 poultry samples were analyzed. Chlorpyrifos was found infrequently in various food types; Table 3-1 lists the chlorpyrifos detections as reported by Duggan et al. (1983).

Published results of the FDA's Total Diet Study list chlorpyrifos as a residue in ready-to-eat foods in only 1 of 14 years in the study. Chlorpyrifos was detected in 2 of 360 food composites that were collected between August 1972 and July 1973. It was found at a concentration of 0.005 ppm in one fruit food composite, and at a concentration of 0.003 ppm in one grain and cereal food composite (Johnson and Manske, 1976).

3.3. INHALATION

Jackson and Lewis (1981) monitored the airborne levels of chlorpyrifos in a test room to which 36 pest control strips (containing a 10% concentration of chlorpyrifos) were applied according to manufacturer's directions. The pest control strips were designed to kill creeping and crawling insects by contact. The test room was meant to be typical of an American home.

TABLE 3-1

Infrequent Detections of Chlorpyrifos in Various Food Products
During Fiscal Years 1970-1976*

Food Product	Total Positive Detections	Year
Small fruits	2	1975
Vine and ear vegetables	7	1975
Root vegetables	1	1976
Whole grains for human use	4	1974
Processed vegetable products	1	1974
Miscellaneous processed food	1	1976
Miscellaneous animal feed	4	1975

*Source: Duggan et al., 1983

Chlorpyrifos levels were monitored by an air sampler and analysed by GC-FPD. Monitored air concentrations of chlorpyrifos are:

Time After Treatment (Days)	Concentration (µg/m³)
Pretreatment	0.03
0.25	0.10
1	0.12
2	0.14
3	0.14
4	0.14
5	0.18
7	0.23
15	0.18
30	0.16

Wright et al. (1981) applied chlorpyrifos as an emulsion spray (0.5% concentration) to cracks and crevices in dormitory rooms at North Carolina State University, and then monitored the ambient air in the rooms following treatment. An average of 1.7 g of chlorpyrifos was applied/room. The airborne average concentration in the rooms before treatment, immediately after treatment and 1, 2 and 3 days after treatment was 0.1, 1.1, 1.1, 0.8 and 0.3 µg/m³, respectively.

Wright and Leidy (1978) applied chlorpyrifos to cracks and crevices of rooms at two different concentrations and, using two application methods, monitored the airborne levels after treatment. The results are summarized in Table 3-2. Wright and Leidy (1980) monitored ambient air levels of chlorpyrifos in the offices and storage rooms of commercial pest control buildings. The mean level in the storage rooms was found to be 220 ng/m³, while the mean level in the office was 126 ng/m³. The mean chlorpyrifos level in the air of vehicles (pick-ups, sedans, vans) used by commercial pest control people was 96 ng/m³. In a study of ambient chlorpyrifos

TABLE 3-2

Chlorpyrifos Levels in Room Air Following Aerosol-Type or Compressed-Air Sprayer Applications to Room Crevices*

Type of Application	Concentration of Spray (%)	Chlorpyrifos Applied/room (g)	Time After Application (days)	Mean Chlorpyrifos Concentration ($\mu g/m^3$)
Aerosol	0.5	0.9	0	1.5
			1	0.1
			2	0.1
			3	0.05
	1.0	1.4	0	2.7
			1	0.2
			2	0.2
			3	0.1
Sprayer	0.5	2.0	0	0.4
			1	0.2
			2	0.2
			3	0.15
	1.0	3.7	0	0.6
			1	0.4
			2	0.35
			3	0.25

*Source: Wright and Leidy, 1978

levels after treatment of spraying of cracks and crevices in food-preparation serving areas, Wright and Leidy (1980) detected concentrations of 20-1488 ng/m³ immediately after spraying, and levels of 4-361 ng/m³ 24 hours after spraying.

3.4. DERMAL

Pertinent data regarding dermal exposure to chlorpyrifos could not be located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

That chlorpyrifos and chlorpyrifos-methyl are readily absorbed by inhalation and dermal, i.p. and oral routes of administration has been demonstrated in a number of organisms.

A metabolite of chlorpyrifos, 3,5,6-trichloropyridinol, was found in the blood (1.4-4.8 ppb) and urine (12-38 ppb) of workers exposed to chlorpyrifos (Takei and Lee, 1981). An extract of liver from a man who ingested a mixture of chlorpyrifos and malathion contained a metabolite of chlorpyrifos involving a methylthio substitution for a chloride in the pyridinol ring (Lores et al., 1978). Hayes et al. (1980) also reported the presence of chorpyrifos and its metabolites in the urine of workers exposed to these chemicals.

Ahdaya and Guthrie (1982) introduced subtoxic levels of ^{14}C-chlorpyrifos (2,6-ring-labeled) to mice by gavage, and monitored the disappearance of ^{14}C from the GI tract. Percentages of ^{14}C absorbed were 15.2, 19.5 and 43.1 at 5, 15 and 30 minutes, respectively. Fitting these data to various kinetic models by computer resulted in a $T_{0.5}$=?8.1±6.2 minutes for ^{14}C absorption. Rats exposed by gavage to a single dose of ^{36}Cl-chlorpyrifos (3,5-^{36}Cl) eliminated 90% of the ^{36}Cl in the urine and 10% in the feces within 74 hours of administration (Smith et al., 1967).

^{14}C from administered ^{14}C-chlorpyrifos ([1-^{14}C]-ethyl labeled) also appeared in the liver, fat, kidneys and urine of mice exposed intraperitoneally to either 5 or 15 mg/kg ^{14}C-chlorpyrifos (Mostafa et al., 1983). Mice exposed dermally to a 1 mg/kg dose of ^{14}C-chlorpyrifos (2,6-ring-labeled) in acetone exhibited a $T_{0.5}$=20.6±5.9 minutes for absorption of ^{14}C from the site of application. Mice exposed similarly to

^{14}C-chloropyrifos-methyl (2,6-ring-labeled) exhibited a $T_{0.5}$=51.6±6.5 minutes for absorption of ^{14}C from the site of application (Shah et al., 1981). Cattle "dipped" in a 0.025% emulsion of chlorpyrifos in water were found to have residues of chlorpyrifos and its oxygen analogue, 3,5,6-trichloro-2-pyridyl phosphate, up to 10 weeks after treatment (Ivey et al., 1972). Metabolic products of chlorpyrifos were recovered in the urine of cows fed 5 ppm chlorpyrifos for 5 days. These metabolites, identified by GC with a flame photometric detector as diethyl thiophosphate and diethyl phosphate, accounted for ~63% of the administered dose and were isolated within 5 days post-treatment (Gutenmann et al., 1968). Chlorpyrifos was also found in the tissues of sheep exposed dermally to 1 mL chlorpyrifos/22.68 kg bw (Ivey and Palmer, 1981).

4.2. DISTRIBUTION

^{14}C was monitored in the tissues of mice exposed dermally to either ^{14}C-chlorpyrifos (2,6-ring-labeled) or ^{14}C-chlorpyrifos-methyl (2,6-ring-labeled) (Shah et al., 1981). Five minutes to 1 hour post-treatment, ^{14}C was found primarily in the carcass, but also in the blood, liver and fat. Eight hours post-treatment, ^{14}C was found primarily in the carcass, intestines, liver and blood, and in trace amounts in heart, lungs, spleen, brain, kidneys, bladder, fat, ear, bone marrow, muscle and stomach.

Chlorpyrifos residues were found primarily in the fatty tissues of cows dipped in a 0.025% of emulsion of chlorpyrifos and water. These data are summarized in Table 4-1. No oxygen analogue was detected in any of these tissues (Ivey et al., 1972). Chlorpyrifos was found in the fat of sheep through 6 weeks after dermal exposure, but was not found in the liver,

TABLE 4-1

Distribution of Chlorpyrifos in Cattle After One Dipping

Time Elapsed After Dipping	Residue* (ppm)	Location
1 week	0.300-0.700	fat
	0.002-0.008	muscle
	0.002-0.003	kidney
	0	liver
2 weeks	0.024-0.291	fat
	0.002-0.003	muscle
	0	kidney
	0	liver
3-4 weeks	0.003-0.145	fat
	0	muscle
	0	liver
	0	kidney

*Similar patterns were obtained for animals dipped 3 and 6 times. For these animals, residues persisted in fat for up to 10 weeks.

kidneys or muscle beyond 2 weeks post-treatment. The oxygen analogue was found in liver and kidneys throughout the examination period, but not in fat or muscle beyond 3 weeks post-treatment (Ivey and Palmer, 1981).

Uptake of ^{14}C by tissues of mice exposed to ^{14}C-chlorpyrifos (2,6-ring-labeled) by gavage was monitored for 60 minutes. Peak percentages of ^{14}C appeared in the blood (10%) after 60 minutes, liver (14-16%) at 60 minutes, intestine (8-10%) for 5-60 minutes, and in the carcass (20%) at 30-60 minutes post-treatment (Ahdaya and Guthrie, 1982).

The distribution of ^{14}C was monitored in the tissues of mice for 192 hours after i.p. exposure to [1-^{14}C] ethyl-labeled chlorpyrifos. These data are summarized in Table 4-2 (Mostafa et al., 1983).

High concentrations of ^{36}Cl were found in the liver (0.069 nmol/kg), kidneys (0.092 nmol/kg), fat (0.031 nmol/kg) and skin (0.025 nmol/kg) of rats exposed to 50 mg/kg chlorpyrifos/^{36}Cl-chlorpyrifos (3,5 ^{36}Cl) by gavage. The ^{36}Cl in these tissues was associated with chlorpyrifos itself; no metabolites were identified (Smith et al., 1967).

4.3. METABOLISM

Metabolites of chlorpyrifos were identified by GC in the urine of workers exposed to this chemical. 0,0-diethyl phosphate was found in 96% of the urine specimans. 0,0-Diethyl phosphorothionate was also found in 28% of the specimens (Hayes et al., 1980; Lores and Bradway, 1977). 3,5,6-Trichloropyridinol was found in the blood and urine of workers exposed to chlorpyrifos (Takei and Lee, 1981).

Smith et al. (1967) reported that metabolites of ^{36}Cl-chlorpyrifos were found in the urine and feces of rats exposed orally to ^{36}Cl-chlorpyrifos. Nearly 100% of the administered ^{36}Cl was recovered in the urine and feces within 74 hours of exposure, but only a trace of this was

TABLE 4-2

Distribution of ^{14}C-Chlorpyrifos in Mice After Intraperitoneal Exposure

Time (hr)	Liver		fat		Kidney	
	5 mg/kg	15 mg/kg	5 mg/kg	15 mg/kg	5 mg/kg	15 mg/kg
6	12.2	20.8	22.3	29.4	2.9	5.1
24	8.7	16.2	8.9	22.8	3.2	7.1
48	7.8	15.0	5.0	22.8	5.7	19.4
192	5.6	9.7	4.1	14.7	12.9	30.6

attributed to chlorpyrifos. Seventy to eighty percent of the administered ^{36}Cl was associated with 3,5,6-trichloro-2-pyridyl phosphate, while 15-20% was associated with 3,5,6-trichloropyridinol.

As discussed in Section 4.1., 62% of the ingested chlorpyrifos was recovered as metabolites in the urine of cows within 5 days of oral treatment. These metabolites were identified by GC with a flame photometric detector as diethylthiophosphate (35.9%) and diethyl phosphate (26.8%). Chlorpyrifos itself was not identified in the urine. Furthermore, chlorpyrifos incubated in fresh rumen (50 µg/100 mL) and in the presence of liver (50 µg/1 g liver in saline) was not metabolized after 6 or 2 hours, respectively (Gutenmann et al., 1968).

The metabolism of chlorpyrifos and chlorpyrifos-methyl in mice was followed by partitioning extracts of radioactive samples between chloroform and water 8 hours after dermal treatment with ^{14}C compounds (2,6-carbon-labeled; 1 µ Ci in 1 mg/kg/dose). For both pesticides, decreased partitioning ratios with respect to the parent compound were observed in blood, fat, liver and excretory products. Metabolites, however, were not specifically identified (Shah et al., 1981).

The possibility of glutathione-mediated degradation of chlorpyrifos and chlorpyrifos-methyl was investigated by Sultatos et al., 1980. In an experiment designed to analyze the 12-fold difference in acute toxicity between chlorpyrifos and chlorpyrifos-methyl, these investigators reported that chlorpyrifos-methyl and the chlorpyrifos oxon were more extensively degraded by a mammalian liver fraction in the presence of glutathione than were chlorpyrifos or the chlorpyrifos-methyl oxon. In an *in vivo* experiment, mice injected intraperitoneally with chlorpyrifos-methyl (1000 mg/kg)

displayed a "marked and prolonged" depletion of hepatic glutathione, whereas mice injected with chlorpyrifos displayed only a "moderate and transient" depletion.

4.4. EXCRETION

The study by Smith et al. (1967) discussed in Sections 4.1., 4.2. and 4.3. gave biological half-lives for ^{36}Cl in various tissues of rats exposed to ^{36}Cl-chlorpyrifos by gavage. These were 10 hours for liver, 12 hours for kidneys, 16 hours for muscle and 62 hours for fat. Control half-lives for ^{36}Cl determined with ^{36}Cl-NaCl were 40-50 hours for liver, kidney and muscle, and 18 hours for fat. Ninety percent of the administered ^{36}Cl was recovered in the urine and 10% in the feces within 74 hours of administration.

Adhaya and Guthrie (1982) reported only traces of ^{14}C in CO_2 expired by mice exposed to ^{14}C-chlorpyrifos (2,6-ring-labeled) by gavage. One percent of the administered ^{14}C was recovered in the urine of these mice 15-30 minutes post-treatment, while 30% was recovered in the urine at 60 minutes post-treatment.

Other studies regarding the excretion of chlorpyrifos, chlorpyrifos-methyl or their metabolites were discussed in Sections 4.1. and 4.3.

5. EFFECTS

5.1. CARCINOGENICITY

Data regarding the carcinogenicity of chlorpyrifos in rats fed diets providing doses of 0.0-3.0 mg chlorpyrifos/kg/day for 2 years are summarized in Table 5-1. Male and female rats (25 animals/sex/group) fed chlorpyrifos at any dose failed to exhibit a significantly higher incidence of tumors when compared with controls (McCollister et al., 1974). Data pertinent to the carcinogenicity of chlorpyrifos-methyl could not be located in the available literature.

5.2. MUTAGENICITY

Data pertinent to the mutagenicity of chlorpyrifos-methyl could not be located in the available literature. Data regarding the mutagenicity of chlorpyrifos are summarized in Table 5-2. The salient feature is that traditional reverse mutation assays performed on various microbial systems yielded negative results regardless of the presence or absence of a mammalian activating system (Waters et al., 1982; Moriya et al., 1983; Gentile et al., 1982). Eukaryotic systems in which chlorpyrifos failed to react with DNA included human lung fibroblasts (Waters et al., 1982) and maize (Gentile et al., 1982). Unscheduled DNA synthesis was monitored in human lung fibroblasts, while reversion from a homozygous waxy genotype to a heterozygous waxy-starchy genotype was monitored in maize. A sex-linked lethal assay with Drosophila melanogaster also yielded negative results.

On the other hand, chlorpyrifos was shown to be genotoxic in some prokaryotic and eukaryotic systems. These data are summarized in Table 5-3.

Waters et al. (1982) reported positive results for a number of differential toxicity assays performed on DNA repair proficient and deficient prokaryotic organisms. These systems included recombination-deficient

TABLE 5-1

Incidence of Tumors in Rats Fed 0-3.0 mg/kg/day Chlorpyrifos for 2 Years*

Tumor Location and Classification	Number of Tumors											
	Males: doses (mg/kg/day) of						Females: Doses (mg/kg/day) of					
	0.00	0.01	0.03	0.10	1.00	3.00	0.00	0.01	0.03	0.10	1.00	3.00
Number of rats examined	25	25	25	25	25	25	25	25	25	25	25	25
Number of rats with tumors	4	2	3	6	3	4	12	6	11	4	8	8
Thyroid	0	0	0	0	0	1	2	0	0	0	0	0
carcinoma	0	0	0	0	0	0	1	0	0	0	0	0
adenoma					1	0	5	2	6	2	3	6
Pituitary	0	0	0	0								
adenoma												
Adrenal	1	1	1	0	0	0	0	0	0	0	0	0
phaeochromocytoma	0	0	0	0	0	1	0	0	0	0	0	0
cortical carcinoma							1	0	0	0	0	0
Pancreas "islet" cell adenoma	0	0	1	0	0	0						
Mammary gland	0	0	0	0	0	0	2	2	2	1	3	3
fibroadenoma	0	0	0	0	0	0	0	0	1	0	1	0
cystadenoma	0	0	0	0	0	0	0	0	1	1	0	0
adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0
adenoma												
Lymphoreticular and hematopoietic	2	1	1	3	1	0	0	2	1	0	1	1
malignant lymphoma	0	0	0	1	0	0	0	0	0	0	0	0
granulocytic leukemia												
Subcutaneous and intramuscular	1	0	0	0	0	0	0	0	0	0	0	0
fibrosarcoma	0	0	0	0	1	2	0	0	0	0	0	0
carcinoma	0	0	0	0	1	0	0	0	0	0	0	0
neurofibroma	0	0	0	1	0	0	0	0	0	0	1	0
retrobulbar undifferentiated sarcoma	0	0	0	0	0	0	0	0	0	0	0	0
undifferentiated sarcoma												
Uterus	NA	NA	NA	NA	NA	NA	1	0	0	0	0	0
adenoma	NA	NA	NA	NA	NA	NA	1	0	0	0	0	0
fibropapilloma	NA	NA	NA	NA	NA	NA	0	0	1	0	0	0
angiomatous polyp	NA	NA	NA	NA	NA	NA	1	0	0	0	0	0
papilloma	NA	NA	NA									
adenomatous polyp												

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TABLE 5-1 (cont.)

Tumor Location and Classification	Number of Tumors											
	Males: doses (mg/kg/day) of						Females: Doses (mg/kg/day) of					
	0.00	0.01	0.03	0.10	1.00	3.00	0.00	0.01	0.03	0.10	1.00	3.00
Number of rats examined	25	25	25	25	25	25	25	25	25	25	25	25
Number of rats with tumors	4	2	3	6	3	4	12	6	11	4	8	8
Liver bile duct adenoma	0	0	0	0	1	0	0	0	0	0	0	0
Central nervous system meningioma	0	0	0	1	0	0	0	0	0	0	0	0
Urinary bladder papilloma	0	1	0	0	0	0	0	0	0	0	0	0
Total number of tumors	4	3	3	6	5	4	15	7	12	4	9	10

*Source: McCollister et al., 1974

NA - Not applicable

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TABLE 5-2

Mutagenicity of Chlorpyrifos

Assay	Species	Strain	Concentration (mg/plate)	Application Method	Activation System*	Response	Reference
Reverse mutation	Salmonella typhimurium	TA100, TA98	0-5	plate incorporation	+/-	-	Moriya et al., 1983
		TA1535, TA1537	0-5		+/-	-	
		TA1538	0-5		+/-	-	
		TA100, TA98	0-10	plate incorporation	+/-	-	Waters et al., 1982
		TA1535, TA1537	0-10		+/-	-	
		TA1538	0-10		+/-	-	
		TA100, TA98	NR	plate incorporation	+/-	-	Gentile et al., 1982
		TA1535, TA1537	NR		+/-	-	
		TA1538	NR		+/-	-	
Reverse mutation	Escherechia coli	WP2 hcr	0-5	plate incorporation	+/-	-	Moriya et al., 1983
		WP2	0-10	plate incorporation	+/-	-	Waters et al., 1982
Sex-linked recessive lethal	Drosophila melanogaster	NR	NR	NR	-	-	Waters et al., 1982

*S-9 fraction in all cases, except Gentile et al. (1982) used both S-9 and Is, a plant activating system isolated from maize.

NR = Not reported

TABLE 5-3

Interaction of Chlorpyrifos with DNA or RNA

Assay	Species	Strain	Method of Application	Dose	Activation System*	Response	Comments	Reference
PolA differential toxicity	E. coli	P3478 W3100	spot test	NR	-	+	NC	Waters et al., 1982
RecA differential toxicity	B. subtilis	M45 H17	spot test	NR	-	+	NC	Waters et al., 1982
Rec⁺/rec⁻ differential toxicity	S. typhimurium	SL4700 SL4525	spot test	NR	-	+	NC	Waters et al., 1982
Differential toxicity	S. typhimurium	TA1538 TA1978	spot test	NR	-	+	NC	Waters et al., 1982
Mitotic gene conversion	S. cerevisiae	D_4	plate incorporation	NR	+/-	-	NC	Gentile et al., 1982
Recombination	S. cerevisiae	D_3	plate incorporation	NR	+/-	-	NC	Waters et al., 1982
Recombination	maize	NR	pre-emergence spray	2.24 kg/ha	NA	-	NC	Gentile et al., 1982
Unscheduled DNA synthesis	human lung fibroblasts	WI-38	tissue culture	NR	+/-	-	NC	Waters et al., 1982
^{14}C incorporation into DNA or RNA	mouse liver	NR	intraperitoneal injection of ^{14}C-chlorpyrifos	5 or 15 mg/kg	NA	+	^{14}C found in DNA and RNA in peak concentrations 6 hours post-treatment.	Mostafa et al., 1983
Sister chromatid exchange	human lymphoid cells	LAZ-007	tissue culture	0.02 µg/mL 0.20 µg/mL 2.00 µg/mL 20.00 µg/mL	+/- +/- +/- +/-	- - + +	Metaphase plates were stained and examined after a 48-hour incubation with chlorpyrifos and 5-bromodeoxypyridine.	Sobti et al., 1982

TABLE 5-3 (cont.)

Assay	Species	Strain	Method of Application	Dose	Activation System*	Response	Comments	Reference
Mitotic Index	human lymphoid cells	LAZ-007	tissue culture	0.02 µg/mL 0.20 µg/mL 2.00 µg/mL 20.00 µg/mL	- - - -	- - + +	Metaphase plates were stained and examined 48 hours post-incubation with chlorpyrifos and 5-bromodeoxypyridine. Number of first, second and third generation metaphases were quantified. Positive response indicates a significantly higher number of M_1 of and significantly lower number of M_3 with respect to controls.	Sobti et al., 1982
Appearance of micronuclei in polychromatic erythrocytes from bone marrow	mice	Swiss	oral	80 ppm 240 ppm 120 ppm	NA	- + +	Mice were treated for 14 days. 10 weeks of treatment, positive results obtained after 2-3 weeks.	Amer and Fahny, 1982
			intraperitoneal	5 mg/kg 15 mg/kg 30 mg/kg	NA	- + +	After single or repeated injections	
			dermal	99 mg/kg	NA	-	14 days of treatment	

*S-9 in all cases, except Gentile et al. (1982) used both S-9 and Is, a plant activating system isolated from maize.

NA = Not applicable

NC = No comment

NR = Not reported

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strains of Bacillus subtilis and Salmonella typhimurium, and a DNA-polymerase-I-deficient strain of S. typhimurium. Positive results were also obtained in the following eukaryotic systems: ^{14}C was incorporated into the RNA and DNA extracted from livers of mice injected intraperitoneally with ^{14}C-containing chlorpyrifos ([1-^{14}C] ethyl-labeled). Peak concentrations were acheived within 6 hours of injection and subsequently decreased with time (Mostafa et al., 1983). When compared with controls, chlorpyrifos (2 or 20 µg/mL) was demonstrated to decrease significantly both the percentage of SCE and the rate of mitosis in human lymphoid cells (Sobti et al., 1982). Mice exposed either orally or dermally to chlorpyrifos exhibited significantly increased numbers of micronuclei in the polychromatic erythrocytes found in bone marrow. The presence of micronuclei is an indication of chromosomal aberrations (Amer and Fahmy, 1982).

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of chlorpyrifos-methyl could not be located in the available literature. In two successive experiments, however, Deacon et al. (1980) investigated the teratogenicity of chlorpyrifos in CF-1 mice. In the first experiment, 51 control dams were administered cottonseed oil by gavage, while groups of 40, 44 and 47 dams were administered 1, 10 and 25 mg chlorpyrifos in cottonseed oil/kg/day by gavage, respectively. Treatment was given on days 6-15 of gestation (vaginal plug indicative of day 0), and observations were made on day 18 of gestation. In this experiment, signs of maternal toxicity including death (4), lethargy and ataxia were observed in dams receiving 25 mg/kg/day, while dams receiving either 10 or 25 mg/kg/day had significantly reduced levels of cholinesterase in both plasma and RBCs when compared with controls. Fetal body weight and crown-rump length were significantly different from controls

only at 25 mg/kg/day. The incidence of skeletal malformations was significantly higher than controls in fetuses from dams receiving 25 or 1 mg/kg/day, but not in those from dams receiving 10 mg/kg/day. Cholinesterase levels in the fetal homogenate were significantly reduced in comparison with controls at treatment levels of 10 and 25 mg/kg/day.

In the second experiment, groups of 41, 35, 36 and 35 dams were gavaged with 0, 0.1, 1.0 or 10.0 mg chlorpyrifos/kg/day, respectively, according to the protocol described for the first experiment. On the 18th day of gestation, there were no signs of maternal toxicity, except for a significant reduction with respect to controls in levels of plasma and red cell cholinesterase in dams treated with 1.0 or 10.0 mg/kg/day. A significant number of litters exhibited delayed ossification of the skull and sternebrae at the two highest levels of treatment, but the number of fetuses affected was not significantly different from controls. In general, no soft tissue or skeletal malformations were seen at any level of treatment. Fetal weight, crown-rump length, or cholinesterase levels were comparable among controls and the various levels of treatment. Chlorpyrifos is thus teratogenic in mice only at levels that produce significant maternal toxicity (25 mg/kg/day).

5.4. OTHER REPRODUCTIVE EFFECTS

Prefreeze and post-thaw measures of sperm quality were quantified in Holstein bulls prior to, 6 months after, and 6-12 months after treatment with chlorpyrifos (Everett, 1982). Prefreeze qualities measured included: original volume of ejaculate, concentration of sperm/ejaculate, percent motile sperm/ejaculate, and percent prefreeze discards. Post-thaw qualities measured included: percent motile sperm and percent discards. Of the 185 bulls treated dermally with chlorpyrifos (43% solution poured over the withers), 7 died, 6 became very sick and 172 suffered no adverse effects.

The 172 bulls that did not become sick showed no significant difference with regard to prefreeze semen quality when compared with untreated controls. These bulls yielded a significantly higher number of post-thaw discards during the first 6 months post-treatment, but returned to normal levels of post-thaw discard in the 6-12 month post-treatment period. The six bulls that became very sick from treatment with chlorpyrifos exhibited a significant decline in prefreeze and post-thaw semen quality. Post-thaw levels returned to normal in the 6-12 month post-treatment period, but prefreeze levels did not.

Data pertinent to other reproductive effects of chlorpyrifos-methyl could not be located in the available literature.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

McCollister et al. (1974) investigated the chronic toxicity of orally administered chlorpyrifos in rats and dogs. Groups of 25 male and 25 female rats were fed diets providing chlorpyrifos at doses of 0, 0.01, 0.03, 0.1, 1.0 and 3.0 mg/kg/day for 2 years. Additional groups of 5-7 rats of each sex were also started on test (specifically when this occurred was not reported) for interim analysis of cholinesterase activity (6, 12, 18 and 24 months for brain ChE; 1 week, 1, 3, 6, 9, 12 and 18 months for plasma and red cell ChE). Cholinesterase activity was also monitored in "selected rats" from each level of treatment after 2 years of exposure. To assess the reversibility of any effect of the toxicant on cholinesterase activity, "some rats" were fed chlorpyrifos at the various levels of treatment for 12 months and then were placed on the control diet 7-8 weeks prior to sacrifice. Autopsies were performed on all rats killed at 12, 18 and 24 months and on those fed the control diet for 7-8 weeks prior to sacrifice. Histological examinations were performed on the major tissues of all rats exposed

to 0 and 3 mg/kg/day, and on any rat that had visible tissue masses or that died prior to termination of the study. Urological and hematological variables were assessed at 6-month intervals for rats exposed to 0, 1.0 and 3.0 mg/kg/day. Clinical chemistry variables were assessed at 12, 18 and 24 months (sacrificed rats only). Dogs were fed comparable doses of chloropyrifos, but in two phases. In phase A, groups of three males and three females were fed diets providing 03.0 mg/kg/day of chlorpyrifos for 1 year. At this time, one male and 0 female/level of treatment were sacrificed and autopsied. The remainder of the animals were placed on the control diet for 3 months, then killed. Cholinesterase activities were measured at 1 week, 1, 3, 6, 9 and 12 months, after 3 months on the control diet (RBC and plasma), and in brain tissue collected at autopsy. In phase B, groups of four males and four females were fed diets providing 0-3.0 mg/kg/day of chlorpyrifos for 2 years. Cholinesterase activity was monitored 2 times before initiation on test and at 1 week, 1, 3, 6, 12, 15, 18 and 24 months on test. All dogs were killed at 24 months and autopsied. Brain ChE and organ weights were measured at this time. Body weight, food consumption, and hematological, urological and clinical variables were quantified periodically for dogs in both phases of the study. Histological examinations were performed on the major tissues of dogs receiving 0 (A and B), 1.0 (A) and 3.0 (A and B) mg/kg/day, and on tissues of dogs receiving lower doses if tissue masses were apparent.

For both rats and dogs there were no compound-related differences between chlorpyrifos-treated animals and controls with regard to mortality, growth rate, food consumption, organ weights, hematological or urological variables and gross or microscopic analysis of tissues. Cholinesterase activity in plasma and red cells was reduced in comparison with controls,

however, in rats exposed to either 1 or 3 mg/kg/day and in dogs exposed to 0.1 (plasma only), 1 or 3 mg/kg/day. Brain cholinesterase activity was reduced in rats (significantly) and dogs (slightly) receiving 3.0 mg/kg/day. Reversal of the depression in cholinesterase activity (brain, red cells and plasma) was observed when chlorpyrifos-treated rats and dogs were placed on control diets. In dogs, reversal was complete within 3 months, while in rats recovery was seen within 8 weeks.

Buchet et al. (1977) fed male Sprague-Dawley rats (number not specified) 100 ppm chlorpyrifos in the diet for a period of 1 year. Total blood cholinesterase, hormone sensitive lipase activity in adipose tissue, lipoprotein lipase activity in adipose tissue, and proteins and lipids in the aorta and serum were measured in rats fed chlorpyrifos and maintained on either normal or fat-rich diets, and in untreated rats maintained on either normal or fat-rich diets. No statistically significant differences were observed between chlorpyrifos-treated and untreated rats for any of these variables.

Workers exposed to chlorpyrifos (mean 8-hour air sample of 6.29 ± 9.97 $\mu g/m^3$), 2 years on the average, exhibited significantly reduced levels of plasma cholinesterase activity when compared with age- and sex-matched controls, but suffered no other apparent adverse effects, though 71% of those examined reported "mild aggravation of common respiratory problems" (Hayes et al., 1980).

5.6. OTHER RELEVANT INFORMATION

Acute toxicity data for chlorpyrifos and chlorpyrifos-methyl are summarized in Table 5-4.

Sultatos et al. (1981) reported a 12-fold difference in acute toxicity between chlorpyrifos and chlorpyrifos-methyl in male mice exposed intraperitoneally to these pesticides (Table 5-4). They tried to account for

TABLE 5-4

Acute Toxicities of Chlorpyrifos and Chlorpyrifos-Methyl

Species	Route of Administration	LD_{50}		Reference
		Chlorpyrifos	Chlorpyrifos-Methyl	
Rat	oral	118-245		McCollister et al., 1974
		132-181 (M) 69-97 (F)		Gaines, 1969
	dermal	176-232 (M)		Gaines, 1969
	subcutaneous		4800 (M)[a]	Hasegawa et al., 1973
	oral		1800 (F)[b] 2500 (M)[b] 3700[a]	Hasegawa et al., 1973
Mice	subcutaneous		2800[a]	Hasegawa et al., 1973
Rats and mice	inhalation oral	83-106 143-162		Berteau and Deen, 1978
Rabbits Guinea pigs	oral oral	2000 504		McCollister et al., 1974
Mice	intraperitoneal	192 (M)	2325 (M)	Sultatos et al., 1982

[a] In carboxycellulose

[b] In corn oil

these differences in terms of differential glutathione-mediated detoxification, but were unable to do so. In an in vitro experiment, chlorpyrifos-methyl and the oxon of chlorpyrifos were more extensively degraded by a liver fraction in the presence of glutathione than were chlorpyrifos or the chlorpyrifos-methyl oxon. Furthermore, mice injected with chlorpyrifos-methyl (1000 mg/kg) displayed a "marked and prolonged" depletion of hepatic glutathione, whereas mice injected with chlorpyrifos did not. Equitoxic doses of chlorpyrifos (70 mg/kg) and chlorpyrifos-methyl (1000 mg/kg), however, resulted in concentrations of chlorpyrifos-methyl in brain tissue which were 46 times higher than those of chlorpyrifos, even though the depression of brain cholinesterase activity produced by these chemicals at these doses was similar (<25% control activity, 8-16 hours post-treatment). Oxygen analogues of chlorpyrifos and chlorpyrifos-methyl were not found in the brain.

Stalberg et al. (1978) reported on a group of 11 Swedish spraymen who regularly handled solutions of organophosphorous pesticides (4% lindane, 0.2% pyrethrum, 0.125% piperonylbutoxide, 2.5% malathion, 2% bromophos in kerosene or 0.5% chlorpyrifos). These men had been employed for 1-24 years and were used as their own controls. Blood and urine samples were taken and neurophysiological exams performed after 1-4 weeks of non-exposure (pre-exposure values) and within 1-24 hours of exposure (duration of exposure was not specified). Relative to pre-exposure values, these men displayed a slight but significant reduction (3%) in nerve conduction velocity and a reduction in plasma but not red cell cholinesterase activity. Aside from an occasional headache, no other symptoms of neurological disorder were reported or observed.

An infant exposed to chlorpyrifos for a period of 8 days displayed symptoms (other than death) similar to those associated with sudden infant death syndrome. The house had been sprayed for termites and roaches, and traces of chlorpyrifos were found on food-preparation surfaces and on the baby's clothing (Dunphy et al., 1980).

An in vitro study using preparations of adrenal tissue from male rats reported that chlorpyrifos (10^{-4} M) inhibited CAMP-stimulated and ACTH-stimulated corticosteroidogenesis by 78 and 66% of control values, respectively (Civen and Brown, 1974).

A 50% inhibition value of 1.8×10^{-2} g/ℓ dilute blood was given for inhibition of human monocyte esterase activity by chlorpyrifos (Dursaban). This value indicated that chlorpyrifos was relatively inactive compared with other organophosphates such as 2,2'-dichlorovinyl dimethyl phosphate (50% inhibition = 2.2×10^{-7} g/ℓ dilute blood) (Lee and Waters, 1977).

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

Data on the acute lethal effects of chlorpyrifos to freshwater fish are abundant (Table 6-1). For a 96-hour-exposure period, LC_{50}s ranged from 2.4 and 7.1 µg/ℓ (ppb) in the sensitive species, bluegill sunfish (Lepomis macrochirus) and rainbow trout (Salmo gairdneri), to 203 and 280 µg/ℓ in fathead minnow, Pimephales promelas, and channel catfish, Ictalurus punctatus, respectively. Macek et al. (1969) demonstrated that ambient water temperature greatly influenced the toxicity of chlorpyrifos. At 1.6, 7.2 and 12.7°C, the respective 24-hour LC_{50} values were 550, 110 and 53 µg/ℓ, a 10-fold variation. Similarly, the 96-hour LC_{50} values at 1.6, 7.2 and 12.7°C were 51, 15 and 7.1 µg chlorpyrifos/ℓ.

Generally, marine species of fish appear to be slightly more sensitive to chlorpyrifos than freshwater species (Table 6-2). The striped bass, Morone saxatilis, was the most sensitive species tested, having a 96-hour LC_{50} value of 0.58 µg/ℓ in 13°C water (Korn and Earnest, 1974). Schimmel et al. (1983) reported that 96-hour LC_{50} values in the Atlantic silverside, Menidia menidia, killifish, Fundulus similus, and striped mullet, Mugil cephalus, were 1.7, 4.1 and 5.4 µg/ℓ. The sheepshead minnow, Cyprinodon variegatus, was slightly more resistant, with a 96-hour LC_{50} of 136 µg chlorpyrifos/ℓ when tested at 31°C. The marine crustacean, Mysidopsis bahia (an important fishfood species), was quite sensitive to chlorpyrifos exposure, having a 96-hour LC_{50} value of 0.035 µg/ℓ at 27°C (Schimmel et al., 1983).

In a study of marine benthic populations exposed to chlorpyrifos, Tagatz et al. (1982) reported a decrease in arthropod and molluskan larvae abundance at levels as low as 0.1 µg/ℓ. Aquaria were established in the

TABLE 6-1

Acute Lethal Effects of Chlorpyrifos to Freshwater Fish

Species	Duration (hours)	Concentration (µg/L)	Method	Effect	Reference
Rainbow trout, *Salmo gairdneri*	48	20	static; 12.8°C	LC_{50}	NTACWQC, 1968
Rainbow trout, *S. gairdneri*	24	53	static; 12.7°C	LC_{50}	Macek et al., 1969
	96	7.1	static; 12.7°C	LC_{50}	Macek et al., 1969
Rainbow trout, *S. gairdneri*	48	11.4	intermittent-flow, 15.6°C	LC_{50}	Holcombe et al., 1982
	72	8.0	intermittent-flow, 15.6°C	LC_{50}	Holcombe et al., 1982
	96	8.0	intermittent-flow, 15.6°C	LC_{50}	Holcombe et al., 1982
Cutthroat trout, *Salmo clarki*	96	18.0	static; 10°C	LC_{50}	Johnson and Finley, 1980
Lake trout, *Salvelinus namaycush*	96	98	static; 12°C	LC_{50}	Johnson and Finley, 1980
Bluegill sunfish, *Lepomis macrochirus*	96	2.4	static; 18°C	LC_{50}	Johnson and Finley, 1980
Green sunfish, *Lepomis cyanellus*	36	37.5	NR	LC_{50}	Ferguson et al., 1966
Fathead minnow, *Pimephales promelas*	24	320	intermittent-flow, 25.1°C	LC_{50}	Holcombe et al., 1982
	48	248	intermittent-flow, 25.1°C	LC_{50}	Holcombe et al., 1982
	72	220	intermittent-flow, 25.1°C	LC_{50}	Holcombe et al., 1982
	96	203	intermittent-flow, 25.1°C	LC_{50}	Holcombe et al., 1982
Fathead minnow, *P. promelas*	96	140	flowthrough; 25.0°C	LC_{50}	Jarvinen and Tanner, 1982
Golden shiner, *Notemigonus crysoleucas*	36	45	NR	LC_{50}	Ferguson et al., 1966
Channel catfish, *Ictalurus punctatus*	96	280	static; 18°C	LC_{50}	Johnson and Finley, 1980

TABLE 6-1 (cont.)

Species	Duration (hours)	Concentration (µg/l)	Method	Effect	Reference
Mosquitofish, Gambusia affinis	24	4,000	static	LC_{50}	Hansen et al., 1972
Mosquitofish, G. affinis	48	5,000	NR	100% mortality	Darwazeh and Mulla, 1974
	120	100	field test	negligible mortality	Darwazeh and Mulla, 1974
Mosquitofish, G. affinis	36	230	NR	LC_{50}	Ferguson et al., 1966
Carp, (unspecified)	24	310	NR	LC_{50}	El-Refai et al., 1976
Carp, (unspecified)	48	4,220	NR	LC_{50}	Jirasek et al., 1978
Tilapia, I. mossambica	96	4.8	NR	LC_{50}	Moorthy et al., 1982
Tilapia, I. mossambica	24	84	NR	LC_{50}	El-Refai et al., 1976
Carassius carassius	48	14,800	NR	LC_{50}	Jirasek et al., 1978
Tinca tinca	48	310	NR	LC_{50}	Jirasek et al., 1978
Leucaspius delineatus	48	40	NR	LC_{50}	Jirasek et al., 1978
Hypophthalmichthys molitrix	48	10,000	NR	LC_{50}	Jirasek et al., 1978
Rhodeus sericeus	48	500	NR	LC_{50}	Jirasek et al., 1978

NR - Not reported

TABLE 6-2

Acute Lethal Effects of Chlorpyrifos to Marine Species

Species	Duration (hours)	Concentration (µg/ℓ)	Method	Effect	Reference
Sheepshead minnow, *Cyprinodon variegatus*	96	136	flowthrough; 31°C	LC_{50}	Schimmel et al., 1983
Striped bass, *Morone saxatilis*	96	0.58	intermittent-flow; 13°C	LC_{50}	Korn and Earnest, 1974
Killifish, *Fundulus similus*	96	4.1	flowthrough; 30°C	LC_{50}	Schimmel et al., 1983
Silverside, *Menidia menidia*	96	1.7	flowthrough; 28°C	LC_{50}	Schimmel et al., 1983
Striped mullet, *Mugil cephalus*	96	5.4	flowthrough; 25°C	LC_{50}	Schimmel et al., 1983
Blue crab, *Callinectes sapidus*	NR	10.0	continuous-flow	100% mortality	Butler and Johnson, 1967
Mysid shrimp, *Mysidopsis bahia*	96	0.035	flowthrough; 27°C	LC_{50}	Schimmel et al., 1983

field and moved to the laboratory for a 1-week-exposure period. Annelid and chordate populations were not affected at levels as high as 8.5 µg/ℓ during the 1-week exposure.

Freshwater invertebrates, crustaceans and juvenile insects, which are important fishfood species, were also more sensitive to chlorpyrifos exposure than were the fish (Table 6-3). The crustacean, Gammarus lacustris, reportedly had a 96-hour LC_{50} value of 0.11 µg/ℓ (Sanders, 1969), and stonefly naiads, Pteronarcella badia and Claassenia sabulosa, had 96-hour LC_{50} values of 0.38 and 0.57 µg/ℓ, respectively. Using an emulsifiable chlorpyrifos-methyl product (22.5% active ingredient), Muirhead-Thomson (1978) reported mortality levels to be several hundred µg/ℓ in several aquatic insect nymphs. These data do not permit a comparison of the aquatic toxicity of chlorpyrifos and chlorpyrifos-methyl.

The sublethal effects of chlorpyrifos (47 µg/ℓ) in fathead minnows, P. promelas, included the disruption of schooling behavior (after 24 hours), stiff vertebral columns and the development of spinal deformities after 48 hours of exposure (Holcombe et al., 1982). Juvenile trout, S. gairdneri, exposed at 5.0 µg/ℓ, developed spinal deformities within 30 hours in areas near the dorsal and caudal fin. Oddly, these deformities were preceded by darkened areas that disappeared when the deformities occurred (Holcombe et al., 1982). Loss of equilibrium was reported in some trout (24%) after 72 hours of exposure at 5.0 µg/ℓ.

6.2. CHRONIC EFFECTS

Jarvinen and Tanner (1982) conducted embryo-larval studies of 32 days duration in fathead minnows, P. promelas. Groups of ~30 embryos (48 hours after hatching) were exposed at 0.9, 1.6, 3.2, 5.7 and 10.2 µg chlorpyrifos/ℓ. Survival was 100% in the control group and in those exposed at

TABLE 6-3

Acute Lethal Effects of Chlorpyrifos/Chlorpyrifos-Methyl to Freshwater Invertebrates

Species	Duration (hours)	Concentration (µg/ℓ)	Method	Effect	Reference
Scud, *Gammarus lacustris*	24	0.76	static; 21°C	LC_{50}	Sanders, 1969
	48	0.40	static; 21°C	LC_{50}	Sanders, 1969
	96	0.11	static; 21°C	LC_{50}	Sanders, 1969
Scud, *Gammarus pulex*	1	50*	flowthrough; 17.5°C	50% mortality	Muirhead-Thomson, 1978
Stonefly naiad, *Pteronarcys californica*	24	50	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
	48	18	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
	96	10	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
Stonefly naiad, *Pteronarcys badia*	24	4.2	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
	48	1.8	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
	96	0.38	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
Stonefly naiad, *Claassenia sabulosa*	24	8.2	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
	48	1.8	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
	96	0.57	static; 15.5°C	LC_{50}	Sanders and Cope, 1968
Mayfly naiad, *Baetis rhodoni*	1	100*	flowthrough; 17.5°C	100% mortality	Muirhead-Thomson, 1978
Caddis fly larva, *Hydropsyche pellucidula*	1	500*	flowthrough; 17.5°C	70% mortality	Muirhead-Thomson, 1978
Caddis fly larva, *Brachycentrus subnubilis*	1	200*	flowthrough; 17.5°C	80% mortality	Muirhead-Thomson, 1978
Agrion sp.	1	100*	flowthrough; 17.5°C	39% mortality	Muirhead-Thomson, 1978
Blackfly larva; *Simulium* sp.	1	50*	flowthrough; 17.5°C	80% mortality	Muirhead-Thomson, 1978

*Emulsifiable chlorpyrifos-methyl compound (22.5% active ingredient) was tested.

0.9 and 1.6 µg chlorpyrifos/ℓ. Mortality among groups exposed at 3.2, 5.7 and 10.2 µg/ℓ was 10, 14 and 44%, respectively. Similarly, mean final body weights of the minnows exposed to chlorpyrifos at ≥3.2 µg/ℓ were significantly ($p<0.05$) lower than controls.

6.3. PLANT EFFECTS

In laboratory studies, chlorpyrifos at 10 and 100 µg/ℓ inhibited the growth of Chlorella vulgaris and Ankistrodesmus falcatus (Brown and Chow, 1975). In field studies, chlorpyrifos at levels as low as 1.2 µg/ℓ have inhibited population growth in A. falcatus, A. spiralis, Dinobyron sp., Tetraedron sp. and Glenodinium sp. (Brown and Chow, 1975; Brown et al., 1976). Growth rates of the green alga, Chlorococcum sp., and the diatom, Amphiprora sp., were significantly ($p<0.05$) inhibited by 10 mg chlorpyrifos/ℓ within 48 hours of exposure (Maley and Ruber, 1983).

6.4. RESIDUE

Chlorpyrifos was reported to be moderately persistent in sediment-water tests, having a half-life of 24 days (Schimmel et al., 1983). The half-life of chlorpyrifos in water only was 4.6 or 7.1 days, respectively, in tests conducted outdoors in ambient sunlight and temperature (22-45°C) or in darkness. Tests also revealed that chlorpyrifos volatilized so that a half-life of <2 days was reported in laboratory tests with 12 hours of fluorescent light (Schimmel et al., 1983).

Neely et al. (1974) reported that the log BCF for chlorpyrifos in mosquito fish, G. affinis, was 2.67. Based on the log octanol/water partition coefficient (4.82), the calculated log BCF was 2.87.

6.5. OTHER RELEVANT INFORMATION

Mosquitofish, G. affinis, avoided water containing chlorpyrifos at ≥100 µg/ℓ with a significant ($p<0.01$) number selecting pesticide-free water

channels (Hansen et al., 1972). The grass shrimp, Paloemonetes pugio, did not discriminate water containing 0.01, 0.1 or 1.0 µg/ℓ (Hansen et al., 1973). Peterson (1976) noted that Atlantic salmon, Salmo salar, exposed to chlorpyrifos at 100-250 µg/ℓ preferred water ~4°C cooler than control fish. The author suggested that fish select a temperature where the pesticide has a lower toxicity, possibly through regulation of metabolic rate. Feeding rate of mosquitofish, G. affinis, was significantly decreased following 48 hours of exposure to 50 µg chlorpyrifos/ℓ (Johnson, 1977).

Smith et al. (1966) reported that chlorpyrifos is absorbed by fish (goldfish) and rapidly metabolized to up to six compounds (not identified). Distribution of chlorpyrifos or its metabolites, followed over a 9-day post-exposure period, was throughout the body, with accumulation most evident in the visceral organs. This study suggests that absorption of chlorpyrifos by aquatic plants and sediments is very rapid and the amount available for absorption by fish would be limited.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Office of Pesticide Programs of the U.S. EPA has established tolerances for residues of chlorpyrifos and its metabolite, 3,5,6-trichloro-2-pyridinol, in or on a variety of raw agricultural commodities, including meats, fruits and vegetables (0.01-3.0 ppm) and tolerances of 1 5-15 ppm for various forages, hays and fodders (Federal Register, 1982; Code of Federal Regulations, 1983a). In addition, levels between 1.5 and 25 ppm are allowable for the oils of citrus, corn, mint and peanut (Code of Federal Regulations, 1983b).

The Office of Pesticide Programs of the U.S. EPA has established an ADI of 0.01 mg/kg/day chlorpyrifos for humans. This was based on the 2-year carcinogenicity/feeding study with rats and dogs (see Section 5.5.). A NOEL was established as 0.1 mg/kg/day, and a safety factor of 10 was included in the calculation of the ADI. The tolerances for chlorpyrifos in or on raw agricultural commodities are such that the theoretical maximum residue contribution in human diet does not exceed the ADI (Federal Register, 1983).

The ACGIH (1984) lists a TWA-TLV of 0.2 mg/m^3 and a STEL of 0.6 mg/m^3 for workers exposed to chlorpyrifos.

Alexander et al. (1982) reported an average odor threshold value of 0.0012 mg/ℓ for chlorpyrifos in water at 60°C.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of chlorpyrifos could not be located in the available literature.

8. RISK ASSESSMENT

Chlorpyrifos was not found to be carcinogenic when administered orally to both male and female rats (0.01-3.0 mg/kg bw/day) for 2 years, nor was it found to be teratogenic when administered orally to mice at a level of 25 mg/kg bw (see Sections 5.1. and 5.3.).

The only widespread significant effect of chronic exposure to subtoxic levels of chlorpyrifos, seen in humans, rats, dogs and mice, is a reversible depression of plasma and red blood cell cholinesterase activities. In one study (McCollister et al., 1974), rats and dogs fed diets providing 3.0 mg chlorpyrifos/kg bw/day also exhibited a significant depression of brain cholinesterase activity, but no external signs of neurological effects and no gross or microscopic changes in the tissues. In this study, no effects other than depression of plasma and red cell cholinesterase activities were seen below the 3.0 mg/kg bw/day level (0, 0.01, 0.1, 1.0 mg/kg bw/day) of treatment. Assuming that depression of brain cholinesterase activity is an adverse effect, but that depression of cholinesterase activity in plasma or red cells (in the absence of adverse symptoms) is not, a NOAEL of 1.0 can be established from these data. Using this value and an uncertainty factor of 100 (10 to account for interspecies extrapolation and 10 for protection of the most sensitive individuals within the human population), an ADI of 0.01 mg/kg bw/day may be calculated. This is consistent with the ADI calculated by the Office of Pesticide Programs using a NOEL of 0.1 and a safety factor of 10 (see Section 7.1.).

Data pertaining to the carcinogenicity and chronic effects of chlorpyrifos-methyl in the available literature are insufficient to make an assessment of potential risks incurred from exposure to this pesticide.

Statements concerning available literature in this document refer to published, quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies of chlorpyrifos, but no change in the ADI for this chemical was warranted.

Although sufficient data for quantitative risk assessment of chlorpyrifos-methyl were not found in the published literature, the CBI Appendix reviews other data from which an ADI of 0.01 mg/kg bw/day, or 0.7 mg/day for a 70 kg human, is derived. The ADI is based on a NOAEL of 1.0 mg/kg bw/day for reduced fertility index in female rats in a 3-generation reproductive study and upon liver effects (weight and histology) and biochemical indices in dogs in a 2-year feeding study. An uncertainty factor of 100 (10 to account for interspecies conversion and 10 for protection of the most sensitive individuals within the human population) was used in the ADI calculation.

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in November, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

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